Clinical and patho-anatomical factors affecting expansion of thoracic aortic aneurysms

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Abstract

Objective—To examine the expansion of aneurysmal aortic segments ($\geq$ 35 mm) and to assess the impact of clinical and patho-anatomical factors on aneurysm expansion.

Design—87 consecutive patients (mean age 63.6 years, range 22–84 years) were studied using serial (six month intervals) computed tomographic or magnetic resonance imaging to monitor progression of thoracic aortic aneurysms. Aortic diameter was measured at seven predetermined segments and at the site of maximum aortic dilatation (MAX).

Results—780 segment intervals were identified. The median overall aneurysm expansion rate was 1.43 mm/year. This increased exponentially with incremental aortic diameter ($p < 0.01$) and varied by anatomical segment ($p < 0.05$). The presence of intraluminal thrombus ($p < 0.01$) but not dissection or calcification was associated with accelerated growth. Univariate analysis identified thrombus ($p < 0.001$), previous stroke ($p < 0.002$), smoking ($p < 0.01$), and peripheral vascular disease ($p < 0.05$) as factors associated with accelerated growth in MAX. Dissection, wall calcification, and history of hypertension did not affect expansion. β Blocker treatment was not associated with protection. Multivariate analysis confirmed the positive effect of intraluminal thrombus and previous cerebral ischaemia, and the negative effect of previous aortic surgery on aneurysm growth. These findings translated into a mathematical equation describing exponential aneurysm expansion.

Conclusions—Aneurysmal thoracic aortic segments expand exponentially according to their initial size and their anatomical position within the aorta. The presence of intraluminal thrombus, atherosclerosis, and smoking history is associated with accelerated growth and may identify a high risk patient group for close surveillance.

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The five year survival of patients with untreated chronic thoracic aortic aneurysms of degenerative or dissecting aetiology has been estimated to be between 13–39%.[1-4] The most common cause of death is aortic rupture which is usually rapidly fatal.[3] Only a fraction of patients initially survive rupture, so allowing time for evaluation and treatment, but the overall salvage rate is low.[5] Elective surgery to repair or replace the aneurysm appears to improve long term survival. However, the operation subjects the patient to significant risk of mortality and morbidity, including the hazard of permanent neurological deficit.[6 7] Rupture is often preceded by a period of rapid aneurysm expansion,[8 9] and detection of this phenomenon could identify patients at high risk of rupture, facilitating the risk–benefit analysis of prophylactic surgical intervention.[10]

In abdominal aortic aneurysms, there are clear size thresholds for when an aneurysm should be considered at high risk of rupture, and there is a correlation between larger aneurysm size, higher expansion rate, rupture risk, and reduced survival.[11 12] The expansion rate of thoracic aortic aneurysms may also reflect the risk of rupture or dissection.[8 10 13] Early studies of the growth of these aneurysms analysed linear expansion rate but more recently formulae that predict exponential growth have been described.[14 15] In these formulae, the aortic expansion rate is related to the initial aneurysm diameter, in concordance with studies of the natural history of abdominal aortic aneurysms.[14 16-19]

Aneurysmal disease is often a multifocal phenomenon within the aorta.[8 20 21] Moreover, aneurysm expansion is three dimensional and three dimensional morphology affects the risk of rupture.[16 22 23] Previous work has focused on the expansion of the maximally dilated segment. The natural history of the remaining aneurysmal aorta is unclear.[24] Furthermore, the effects on aneurysm expansion of clinical and pathoanatomical features, such as the presence of dissection, thrombus, calcification, and previous surgical reconstruction of remote aortic segments, remain unknown.

Our study aimed to investigate the impact of various factors that might influence the expansion rate in our population of patients with thoracic aortic aneurysms. We examined growth in aneurysmal segments both at the maximally dilated area and in other predetermined aortic segments (table 1), and we derived a mathematical formula that describes aneurysm growth in this sample population.

Methods

A review was undertaken of serial imaging studies in consecutive patients undergoing follow up surveillance of aneurysmal segments in the thoracic aorta at a dedicated (thoracic) aortic clinic between January 1991 and February 1998. The arbitrary minimum time interval between scans for study inclusion was six

Table 1 Definitions for the aortic segments studied

Code	Aortic segment studied
A	Mid-ascending aorta
B	Mid-aortic arch*
C	Proximal descending thoracic aorta (proximal to carina)
D	Descending thoracic aorta at level of carina
E	Aorta between carina and diaphragmatic hiatus
F	Aorta at level of diaphragmatic hiatus
G	Aorta at level of superior mesenteric artery
MAX	Dimension of maximally dilated segment

*Measured in the section below the mid-point of the take off of the epiaortic vessels.

months. All patients who had serial scans allowing aneurysmal segment comparison were eligible. The sample also included patients with coexistent aneurysms following surgical repair of other aneurysmal aortic segments.

Imaging was performed using contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Aortic outer diameter was measured using a calliper method and with the reference measurement tool within the scan image. In the case of an elliptical cross section, the minor diameter of the ellipse was measured, regardless of orientation, to avoid convolution effect in an elongated, tortuous aorta.[16][25] Many patients had no suitable reference segment of aorta so for the purpose of this study a segment was defined as aneurysmal if the minor aortic diameter was ≥ 35 mm, in accordance with other studies.[10][16][26][27] Segments showing chronic dissection were also studied, regardless of their initial diameter.

All examinations were analysed retrospectively by one observer, who was unaware of the patient's clinical details. In addition to the diameter of the maximally dilated segment (MAX), aortic outer diameter was also measured at seven predetermined levels (table 1). To assess growth, measurements were undertaken in matched segments between initial and subsequent scans. Segment matching on separate scans was undertaken by identification of
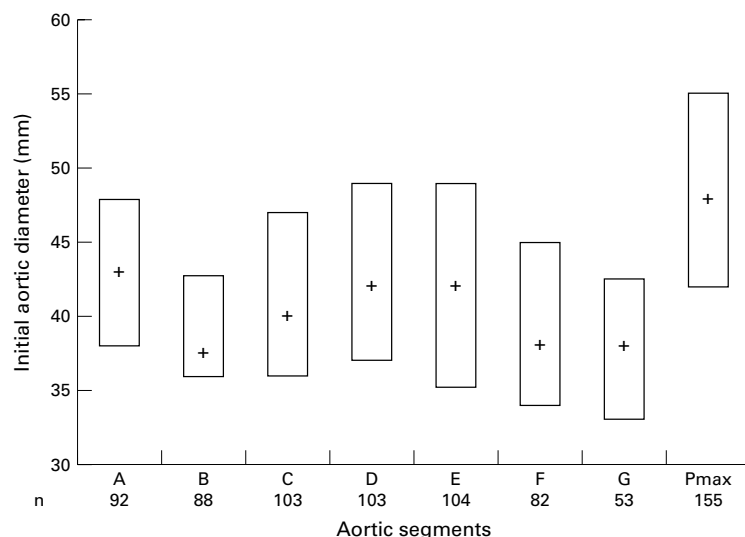

Figure 1 Box plot (median and interquartile range), showing distribution of initial aortic diameter throughout the segments studied (see table 1 for segment code). p < 0.05 (Kruskal–Wallis); n = number of segments.

anatomical landmarks—for example, tracheal carina or superior mesenteric ostium. If matching was not possible, the segment was excluded from the study. If patients had more than two consecutive scans, each segment interval of more than six months was used as a separate comparison.

Baseline scans were examined for evidence of dissection, calcification, or thrombus. Dissection was defined as the presence of an intimal flap or dual lumen, regardless of aortic diameter. This was almost invariably in the context of a clinical history compatible with previous acute dissection or unequivocal initial diagnosis. Calcification was defined as the presence of discrete radio-bright changes in the image of the aortic wall. Thrombus was defined as the presence of circumferential or crescentic non-enhancing filling defect within the aortic lumen on contrast enhanced scans. The patients' case records were retrospectively scanned for the following clinical information: history of active smoking at the time of first assessment; β blocker treatment; hypertension (treated or untreated); previous aortic surgery, either proximal or distal to the segments studied; peripheral vascular disease, defined as either previous intervention or absent lower limb pulses with or without symptoms; treated or previously diagnosed chronic obstructive airways disease; previous transient ischaemic attack or stroke; treated ischaemic heart disease, diabetes mellitus, or Marfan syndrome. A history of non-specific chronic back pain, not felt clinically to be related to the aneurysm, was also included. These data were obtainable from a minimum clerking dataset collected for each patient at the time of the first clinic consultation.

STATISTICAL ANALYSIS

In a pilot study of 50 segment images, analysis of repeated measurements of the minimum aortic diameter at two different measurement occasions showed a coefficient of repeatability of 2.25.[25] Repeatability analysis was performed as described by Bland.[28] From the measurements obtained, a linear expansion rate (ER) and percentage expansion rate (%ER) were calculated as follows: ER = [(last diameter) − (initial diameter) (mm)]/(interval) (years). %ER = ER/(initial diameter) × 100.

For each group, data are expressed as median (range). As each group had expansion rate distributions skewed towards higher expansion rates, we used non-parametric methods for analysis of the apparent effect of individual clinical factors and anatomical variables on expansion rate. In particular, Kruskal–Wallis or Mann–Whitney tests were used to compare the effect of differing segment sizes or sites and the effects of such dichotomous pathoanatomical variables as dissection, calcification, thrombus, and previous aortic surgery. In this context, such comparisons can only give broad indications of the association of individual factors with expansion rate as they may be affected by interacting and confounding factors or by non-linearity of growth, interpatient variation, and intrapatient correlation. In
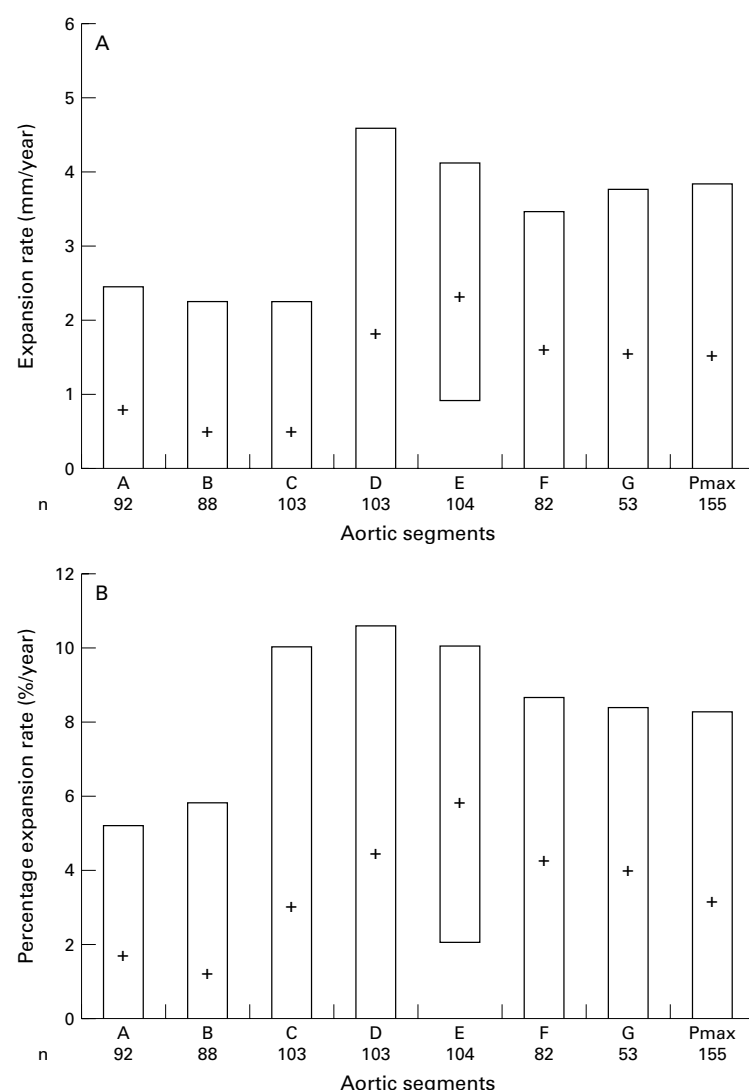
Figure 2   Linear (A) and percentage (B) expansion rate according to segment level (see table 1 for segment code). p < 0.01 (Kruskal–Wallis); n = number of segments.

Our data confirmed the findings of Hirose and colleagues that diameter and expansion rate tend to increase exponentially with time and have skewed distributions.[18] The clinical factors and other variables were therefore entered into a stepwise multiple regression analysis of the logarithm of expansion rate of maximally dilated segments in order to identify significant combinations associated with expansion rate. The regression results can then be transformed into an exponential equation describing growth in this sample incorporating the effect of time and other factors associated, directly or indirectly, with expansion rate. Significance was assigned to those comparisons in which p < 0.05.

Results

Serial comparable scans containing aneurysmal or dissected segments in the baseline study were available in 87 of 153 patients (52 men, 35 women; mean age 63 years, range 22–84 years). Forty patients had a single set of interval scans, 34 had two sets, and 13 had multiple scans for comparison. Fifty one patients had non-dissecting aneurysms, 30 had chronically dissected segments, and six had mixed dissection and degenerative aneurysmal segments. Forty nine patients had undergone previous aortic surgical procedures. The 780 segment intervals identified were distributed as follows: 490 aneurysmal segments without dissection (degenerative), median diameter 43 mm, range 35–97 mm; and 290 segments with dissection, median diameter 38 mm, range 20–73 mm (p < 0.01).

INITIAL AORTIC SIZE AND EXPANSION ACCORDING TO ANATOMICAL SITE

There was a significant overall variation in the initial aortic diameter according to the anatomical position within the aorta (p < 0.05) (fig 1). Further analysis showed that this variation in initial diameter was observed mainly in aneurysms without dissection (p < 0.01) and not in segments with dissection. Initial diameters of the ascending aorta (segment A, table 1) and of the middle part of the descending aorta (segments D and E, table 1) were larger than those of the mid-arch (segment B, table 1) or the thoracoabdominal aorta (segments F and G, table 1) (p < 0.05) (fig 1).

Linear expansion rate was examined before a more robust exponentially based analysis. The linear expansion rate of all segments studied was 1.4 mm/year (range −6.9 to 40.7) and the overall proportional expansion was 3.4%/year (range −13.1% to 107.2%) (fig 2). Absolute and percentage expansion rates varied according to the anatomical position of the segments within the aorta (p < 0.05). Segments within the mid-portion of the descending aorta (segments D and E) showed the most rapid growth. The ascending aorta (segment A) had the lowest expansion rate despite the greatest initial diameter. Absolute and percentage expansion rates of the aortic segments distal to the arch (segments C, D, E, F, and G) were greater than those of the proximal aorta.

the main multivariate analysis, the expansion rate in the maximally dilated segment was used. This avoids correlation effects of using different segments from the same subject.
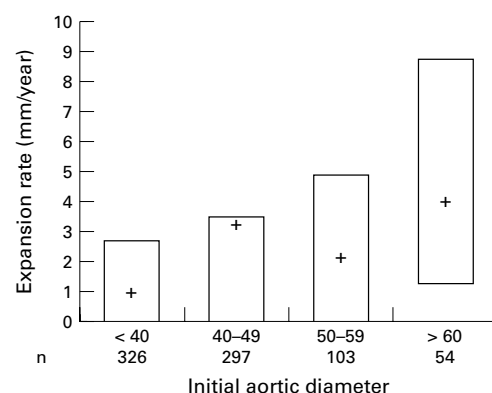

Figure 3   Expansion rate according to initial aortic diameter: p < 0.001 (Kruskal–Wallis). Segments with initial diameter ≥ 60 mm manifested a median expansion rate of 4 mm/year, while smaller aneurysms (< 50 mm diameter) had a median expansion rate of 1.33 mm/year (p < 0.01); n = number of segments.
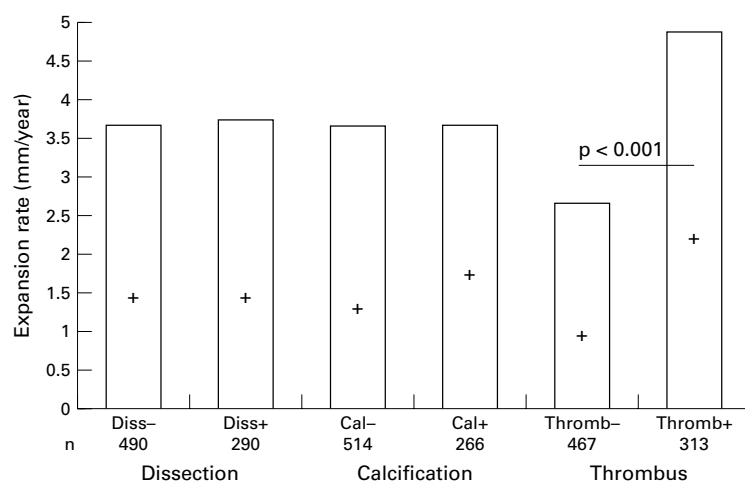
Figure 4 Comparison of expansion rate according to presence (+) or absence (−) of dissection, calcification, and intraluminal thrombus for all segment intervals studied. Thrombus was associated with significantly greater expansion rate (p < 0.01) (Mann–Whitney); n = number of segments.
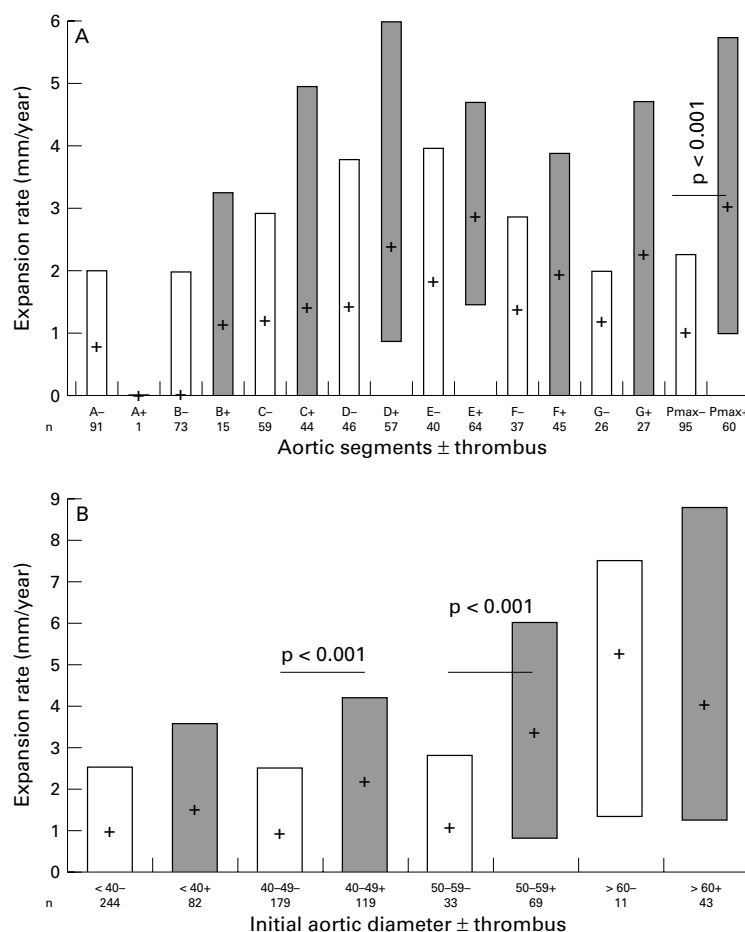

Figure 5 (A) Effect of thrombus on expansion rate by segment (see table 1 for segment code). There is a consistent expansion effect across all segments. (B) Effect of thrombus on expansion according to initial diameter. n = number of segments.

FACTORS AFFECTING EXPANSION RATE IN ALL SEGMENTS

The expansion rate increased with incremental initial diameter (p < 0.001) (fig 3). An association between the presence of thrombus within the aortic lumen and accelerated expansion was detected (p < 0.001), whereas the presence of dissection (p = 0.12) or calcification (p = 0.18) did not affect aneurysm growth (fig 4). The effect of thrombus was observed as a persistent tendency across all aortic segments (fig 5A) and was also consistent with increasing aortic size (fig 5B).

A history of previous aortic surgery (proximal or distal to the segments studied) was associated with a reduced expansion rate: 1.18 mm/year (range −6.9 to 40.7 mm/year) *v* 1.59 mm/year (range 0 to 32.1 mm/year) (p < 0.02). However, on the baseline scans the aortic diameter segments in patients who had undergone previous aortic surgery (proximal or distal to the segments studied) were smaller than in those without previous aortic surgery, at 40 mm (range 20 to 71 mm) *v* 43 mm (range 35 to 97 mm) (p < 0.01).

FACTORS AFFECTING GROWTH IN MAXIMALLY DILATED AORTIC SEGMENTS

Univariate analysis showed that peripheral vascular disease, transient ischaemic attacks or stroke, smoking, and possibly chronic obstructive pulmonary disease (p = 0.06) were associated with increased expansion (table 2). The presence of aortic dissection, wall calcification, and β blocker treatment was not associated with aneurysm growth. The impact of Marfan syndrome (three patients) and diabetes mellitus (four patients) on aneurysm growth could not be analysed owing to the limited number of patients with these conditions and eligible serial scans in our series.

Stepwise multivariate regression analysis of the logarithm of expansion rate indicated the presence of thrombus as the dichotomous variable (p < 0.001) most strongly associated with accelerated expansion. Previous cerebrovascular insult (p < 0.002) was also associated with an increased rate of expansion. Previous aortic operation (p < 0.02) was associated with reduced growth. These findings led to the construction of the following mathematical model of exponential growth relating final aortic diameter (ADf) to initial size (ADi), time interval (years), and the dichotomous variables thrombus, previous aortic operation (prevoper), and transient ischaemic attack/stroke (TIA/Str):

$$ADf = ADi \times e^{(time \times factors)},$$

where factors = (0.0433 + (0.0291 [0.007] × thrombus − 0.0243 [0.007] × prevoper + 0.0215 [0.010] × TIA/Str)) (standard deviations for the coefficients are given in square brackets).

From this formula, the expansion rate of a 44 mm aneurysm in a patient without previous operation or transient ischaemic attack/stroke is calculated as 1.9 mm without a thrombus and 3.3 mm with thrombus. The correlation between observed and predicted expansion rate values is 0.43, which reflects the fact that growth patterns for large aneurysms are more variable than for small, and the model fits best for aneurysm sizes of less than 60 mm. The average error in predicting final size was 0.2 mm with a standard deviation of 2.6 mm, range −5.7 to 11.4 mm.

Table 2 Univariate analysis of factors influencing growth in maximally dilated aortic segments

	Factor	Analysable segments	Median difference*	95% CI	p Value
No effect	Sex	M91; F64	0.00	−0.08 to 0.4	0.68
	Dissection	51/104	−0.13	−0.2 to 1.0	0.13
	Calcification	41/114	0.43	−0.1 to 1.3	0.18
	β Blockade	63/92	0.01	−0.38 to 0.79	0.59
	IHD	50/105	0.00	−1.01 to 0.40	0.61
	Pain	29/126	0.03	−0.30 to 0.99	0.46
	Hypertension	111/44	0.30	−0.02 to 0.97	0.24
Accelerate growth	Thrombus	60/95	1.56	0.78 to 2.45	< 0.001
	TIA/stroke	24/131	2.10	0.57 to 3.70	< 0.002
	Smoking	89/60	0.89	0.17 to 1.70	< 0.01
	PVD	38/117	0.82	0.01 to 1.88	< 0.05
	COPD	34/121	0.96	0.02 to 2.24	0.06
Protect	Aortic surgery	94/61	−0.89	−0.01 to −1.84	< 0.02

95% Confidence intervals (CI) for median difference and p value (Mann–Whitney).
*Median difference represents the effect of each factor on median expansion rate. Thus the presence of thrombus is associated with an expansion rate increase of 1.56 mm/year in segments of the same size.
COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease; PVD, peripheral vascular disease.

Discussion

In accordance with previous studies we observed that thoracic aortic aneurysms enlarge exponentially, and this pattern is consistent in the maximally dilated segment and in other coexistent aneurysmal segments.[16–18] The expansion rate of degenerative aneurysms differs according to their anatomical location. Aneurysmal segments of the descending aorta show an accelerated rate of growth compared with more proximal dilated segments, regardless of their initial dimension. We also found that the level of maximum dilatation within an individual aneurysm could change over time, indicating differential radial expansion throughout the aorta. Thus expansion within individual segments of the same aneurysmal aorta may be static or may accelerate or decelerate.[18 29] The aneurysmal aortic wall appears, therefore, to be a dynamic biological structure with a varying response to its physical environment. This confirms the descriptive value of whole aorta imaging using three dimensional reconstruction to assess aneurysm expansion in terms of cross sectional areas or diameter, length, and volume.[16 18]

Differences in expansion rate according to aneurysm site have been reported previously. Hirose and colleagues detected the most accelerated expansion (even when expressed as percentage growth rate) in the aortic arch.[14] Our results are at variance with their findings and suggest a more rapid expansion in the distal aorta, even though the initial diameters of the 88 arch segment intervals examined are comparable between the two series. The reasons for these differences are unclear but could be related to different sample population characteristics, including pathology and risk factors that could affect expansion rate, and the more extended examination period in the Japanese study. In addition, measurement of the arch segment diameter is known to be prone to error because of the tangential sections on computed tomography.[16] On the other hand, our findings are concordant with those of Coady and associates, who also described higher expansion rates in the descending aorta.[17] In that study, the greatest expansion rate occurred in the proximal descending aorta just distal to the aortic arch. This is also one of the sites of predilection for acute aortic dissection and may reflect the additional haemodynamic stress in this part of the aorta.[30]

Our data do not support the suggestion that the suprarenal abdominal aorta may be protected from expansion by the circumferential wrapping of the diaphragmatic crura.[14] Previous studies have shown different expansion rates above and below the diaphragm and have attributed these to anatomical differences in aortic wall structure.[14 31 32] Unfortunately in our present series there were very few infrarenal aneurysmal segments eligible for the study, and we could not further analyse the differential expansion rate between thoracic and abdominal aneurysmal segments.

The reported expansion rate for maximally dilated aneurysmal segments ranges between 1.2 and 4.3 mm/year,[14 17 19 31 33] and was 2.6 (0.27) mm/year (mean (SD)) in our study. These differences can be attributed to differing aortic initial diameters between series, as the overall pattern of growth in different sample populations is similar.[19] However, the expansion rate of aneurysms of ≥ 60 mm initial diameter (5.6 (0.81) mm/year) detected in our patients was not dissimilar to that reported by others.[16]

The presence of chronic dissection did not affect expansion rate in our study, but this remains an area of controversy.[16 17] Several reports have suggested that the presence of dissection reduces survival and increases rupture rate.[1–3] However, these reports included patients with either acute dissections or technically inoperable disease, thus resulting in an exaggerated early mortality hazard. It is also possible that chronic dissection of the ascending aorta confers an increased risk of both expansion and rupture.[17] In the current study there were very few dissected ascending aortic segments available for analysis. However, in the descending aorta, dissection did not affect growth rate, although the initial diameter of dissected segments was lower (reflecting the inclusion criteria). These observations are important as they suggest that clinical guidelines for intervention may not need to be more aggressive for chronic dissecting thoracic aortic aneurysms.[34]

Previous aortic surgery in segments proximal or distal to the one studied appeared to protect against expansion. While this finding could largely be explained by the smaller initial diameter of the aneurysm in the patients with previous surgery, it was consistent for maximally dilated segments. It is interesting to speculate that aortic wall stress in nonoperated segments may be reduced by previous anatomical reconstruction.

It is difficult to explain why patients with peripheral vascular disease or with previous transient ischaemic attacks or cerebrovascular accidents have an increased expansion rate. MacSweeney and colleagues have shown an increased prevalence of abdominal aortic aneurysm in patients with cerebrovascular

disease.[35] It is possible that more widespread atherosclerosis is associated with more aggressive aneurysm pathology, and that degenerative aneurysms represent a spectrum of heterogeneous vascular dilating diseases. This may explain the increased expansion rate seen in these patients.

The presence of wall calcification is believed by some to protect against expansion and rupture, but this remains controversial.[36] We found that calcification was associated with a higher expansion rate but this was not significant. This is in accordance with previous reports and confirms that calcification does not prevent expansion.[31] Although rupture does not occur through calcified plaques, it can occur through adjacent aortic wall. Therefore in these cases the same criteria for clinical management as for non-calcified aneurysms could apply.

In our patients the presence of mural thrombus was consistently associated with a greater rate of expansion. This confirms the observations of Wolf *et al* and Krupski *et al* in abdominal aortic aneurysms,[37] [38] but is at variance with the observations of Pillari *et al* in large (> 7 cm) aneurysms.[39] As noted below, the interpretation of aortic diameter in the presence of thrombus is difficult. We believe that thrombus may promote expansion for three reasons. First, clinical observation suggests that the aortic wall overlying thrombus is often thinner than in segments not covered by thrombus and is thus potentially more vulnerable to stress forces.[22] By La Place's law—in which $T = (P \times r)/2t$, where T is wall tension, P is the distending pressure, r is the radius, and t is wall thickness—any reduction in wall thickness results in an increase in wall tension, a prerequisite for aneurysm expansion. Second, the aortic wall overlying thrombus may be intrinsically weaker than non-thrombosed aortic wall of comparative thickness. Third, thrombus is often found in convoluted and large volume aortic segments and its formation may be secondary to reduced blood velocity and relative stasis. In such a convoluted aorta, coronal imaging usually results in an elliptical aortic outline. Measurement of the minimum aortic diameter in this situation may underestimate the real dimension exposed to the distending force. Thus such segments may be inadvertently assigned to a lower initial diameter category, leading to an observed discrepancy in measured growth rate.

The presence of a hypertensive history and the use of β blocker treatment were not associated with differential expansion rates. Although these data are consistent with previous reports they should be considered cautiously, as all hypertensive patients were undergoing treatment during the study and therefore adequate blood pressure control could nullify any positive expansion effect of this variable.[16] In addition, it is possible that the mild expansion effect observed in association with chronic obstructive airways disease represents an inability to prescribe β blockers in these patients. Smoking history showed a consistently positive effect on aneurysm expansion, in accordance with other studies, and may reflect the adverse effect of smoking on connective tissue previously shown in abdominal aortic aneurysms.[16] [40–42] These data support the need for smoking cessation advice in such patients.

We did not find that the presence of "non-specific" back pain was associated with expansion. However, in other studies pain has been related to the risk of rupture.[23] This discrepancy could have various causes, but may indicate that patients with pain had already undergone surgery.

STUDY LIMITATIONS

One of the limitations of this study common to previous reports is the referral based nature of the patient population. Thus it remains questionable whether the findings could be extrapolated to patients with clinically silent aneurysms. The study does not allow us to determine the risk of rupture in the individual patient but may nevertheless identify high risk groups needing more frequent surveillance. Only one of the aneurysms in this study ruptured (just before a scheduled admission for surgery). A further limitation is the possibility of measurement error. Scans (CT and MRI) from diverse referral sources were compared with scans from within the institution, and no protocol was in place to determine the number of cross sectional levels for any particular scan. Moreover, the accuracy of the measurement tool within each scan was not determined and segment matching was dependent upon identification of other anatomical structures. We sought to minimise error by using and validating a standardised measurement technique with a single observer.[25]

Only three patients had Marfan syndrome so it was not possible to examine the specific effect of this and other connective tissue disorders on the expansion rate.

As 47 of the 87 patients had two or more pairs of scans it is possible that patients with non-expanding aortas skew this analysis and accentuate the effects of the variables affecting growth rate. Additionally, there could well be an interdependence that determines aneurysm segment growth according to dimensions at a separate site in the same patient. Larger population based studies will be required to answer this criticism.

The expansion rate in very large (6–7 cm) aortas is difficult to establish, as many are operated on before a matched pair of scans is obtained. Nevertheless the stepwise increase in expansion rate with increasing aortic diameter at smaller initial diameters would imply that these patients are at the greatest risk.

The growth rate of aneurysmal segments of the thoracic aorta appears to be dependent on several factors. This information should aid the design of studies to evaluate novel treatments that may prevent or retard aneurysm expansion.

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